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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/296,264	04/22/1999	JIM A. WRIGHT	032396-043	8152

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Lisa A. Haile, Ph.D
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive
Suite 1100
San Diego, CA 92121-2133

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/296,264	WRIGHT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,17-19,23-25,30-45,47-59 and 61-64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *6-9,17-19,23-25,30,32,42-45,47-51,57,59 and 61* is/are allowed.

6)☒ Claim(s) *1,4,5,31,33-41,43,52-56 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-7-05.

Claims 1, 4-9, 17-19, 23-25, 30-45, 47-59, 61-64 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4-7-05 has been entered.

Response to Arguments and Amendments

Withdrawn Objections and Rejections

Any objections or rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 52-56 and 58 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement over the scope claimed, for the reasons of record set forth in the Office action mailed January 15, 2003, August 26, 2003 and August 5, 2004.

Applicant's arguments filed 4-7-05 have been fully considered but they are not persuasive.

Applicants argue that the specification is fully enabling for inhibiting the metastasis of melanomas in vivo using antisense against human neuropilin mRNA. Applicants have also argued that one skilled in the art could make or use the invention from the disclosures in the patent and information known in the art without undue experimentation. Applicants are enabled for a method of inhibiting human tumor growth in vivo (and inhibiting tumor cell growth in vitro) comprising the systemic administration of the antisense oligonucleotides of SEQ ID Nos: 1-3, 5, 6, 8-12 (e.g. of 20-50 nucleobase lengths), and of antisense oligonucleotides of this size range that specifically target and inhibit human neuropilin of SEQ ID NO: 33. Applicants are not enabled for a method of inhibiting the metastasis of melanomas in vivo comprising the administration of antisense oligonucleotides in vivo. The instant disclosure teaches an inhibition of metastasis of tumor cells that had been transfected in vitro with the antisense oligonucleotide of SEQ ID NO: 2 prior to administration of tumor cells in vivo. Tumor cells that had been previously transfected in vitro with antisense oligonucleotides are not considered to be representative or correlative of antisense oligonucleotide delivery in vivo and further whereby metastasis is inhibited. Likewise, inhibition of colony formation in vitro is not representative of inhibition of metastasis in vivo. Enablement for metastatic inhibition comprising the administration of antisense oligonucleotides in vivo would require undue experimentation beyond that provided in the instant disclosure: Adequate concentrations and the appropriate cellular delivery

(i.e. in concentrations required to achieve inhibition of metastasis) of antisense oligonucleotides to potentially metastatic target cells must be addressed using in vivo conditions. The conditions used to deliver adequate concentrations of inhibitory antisense oligonucleotides to tumor cells in vitro, and subsequently inject, previously transfected tumor cells into an animal, are not necessarily correlative with the in vivo delivery of antisense whereby metastasis is inhibited in that organism.

New Rejections

Claim Rejections - 35 USC § 103

Claims 1, 4, 5, 31, 33-41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over He et al and Soker et al in view of Milner et al and Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotides (including vectors that contain antisense sequences) that specifically target and inhibit the expression of SEQ ID NO: 33 encoding human neuropilin in vitro, which antisense are nuclease resistant and are in pharmaceutical compositions, and which antisense optionally comprise one or more phosphorothioate internucleotide linkages, a morpholino backbone structure, a peptide nucleic acid, a modified base (e.g. hypoxanthine), alkyl or heterocyclic intersugar linkages, a 2'-O-substituted ribonucleotide.

The references cited in this rejection were provided in the Office action mailed 8-26-03.

The claimed invention is drawn to compositions comprising antisense oligonucleotides (including vectors that contain antisense sequences) that specifically target and inhibit the expression of SEQ ID NO: 33 encoding human neuropilin in vitro, which antisense are nuclease resistant and are in pharmaceutical compositions, and which antisense optionally comprise one or more phosphorothioate internucleotide linkages, a morpholino backbone structure, a peptide nucleic acid, a modified base (e.g. hypoxanthine), alkyl or heterocyclic intersugar linkages, a 2'-O-substituted ribonucleotide.

He et al teach the nucleotide sequence encoding SEQ ID NO: 33, human neuropilin (See entire document, especially first full paragraph on right on page 740; figure 3 on page 743; second full paragraph on left on page 748; and accession # AF018956). He et al also teach the inhibition of neuropilin to repel sensory axons using anti-neuropilin antibodies, implicating neuropilin as a receptor in neurite outgrowth (e.g. in inducing collapse of growth cones) (pages 739-740; page 744, first full paragraph; figure 4 on page 744; figure 7 on page 747). He also teaches a role of neuropilin in nonneuronal developmental processes including organogenesis, including by correlating morphological abnormalities in nonneural tissues following ectopic expession of neuropilin in transgenic mice (pages 739-740; page 744, last full paragraph).

Soker et al teach the correlation between angiogenic factors, including various VEGF isoforms, and vascularization-dependent tumor growth (see pages 5761-5762). Soker et al also teach the motivation to study the various affinity/molecular mass VEGF

receptors, including neuropilin or $VEGF_{165}$, with respect to their biological roles in tumor vascularization and metastasis (see page 5766, last 3 full paragraphs).

The primary references of He et al and Soker et al do not teach antisense oligonucleotides that target and inhibit the expression of SEQ ID NO: 33 encoding neuropilin in vitro, nor pharmaceutical compositions comprising these antisense, nor the incorporation of phosphorothioate internucleotide linkages, morpholoino backbone structures, peptide nucleic acids, modified bases, alkyl or heterocyclic intersugar linkates, or 2'-O-substituted ribonucleotides in antisense.

Milner et al teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of a target nucleic acid of known nucleotide sequence (See especially figures 5-7 on pages 539-540). This combinatorial technique taught by Milner allows for a simultaneous assessment - by routine empirical screening methods - of all possible oligonucleotides within a given region to inhibit target gene expression (e.g. see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence.").

Baracchini et al teach the administration of pharmaceutical compositions comprising antisense oligonucleotides to appropriate cells in vitro to inhibit target gene expression and target cell growth (e.g. see examples 4 and 5, col. 17-18 of Baracchini

for the use of cellular assays for the routine determination of antisense inhibitory activity). Baracchini et al teach the incorporation of one or more phorphorothioate internucleotide linkages, a morpholoino backbone structure, a peptide nucleic acid, a modified base (e.g. hypoxanthine), alkyl or heterocyclic intersugar linkages, 2'-O-substituted ribonucleotides into antisense oligonucleotides to render the antisense nuclease resistant (See col. 6, line 35-col. 8, line 62; col.17 and 18).

One of ordinary skill in the art would have been motivated to inhibit the expression of neuropilin in vitro because He teaches the role of neuropilin in neurite outgrowth in vitro by generating changes in neurite outgrowth following inhibition of neuropilin receptor activity using antibodies and Soker et al implicate neuropilin in cellular proliferation, including in cancer cell growth. He also teaches the motivation to study neuropilin expression in developmental processes by teaching the generation of morphological abnormalities associated with the ectopic expression of neuropilin. One of ordinary skill in the art would have been motivated to design and assess antisense oligonucleotides for their ability to inhibit the expression of neuropilin in vitro because He teaches the involvement of neuropilin in the molecular mechanisms such as axon repulsion in axonal development using inhibitory antibodies (see first paragraph on page 740), and one would have been motivated to study the participation of neuropilin in these biological processes by inhibiting its expression.

One of ordinary skill in the art would have been motivated to study the biological role of neuropilin because both He et al and Soker et al teach the role of neuropilin in organogenesis, and tumor vascularization and/or metastasis respectively. One of

ordinary skill in the art would have been motivated to study the biological role of this molecule in cellular process by inhibiting its expression because expression inhibition is a routine approach utilized by cell biologists to study a particular molecule's participation or effect on a biological process. One of ordinary skill in the art would have been motivated to generate antisense oligonucleotides to inhibit neuropilin expression because He teaches the nucleotide sequence encoding neuropilin, and a routine and well known way of studying the role of a molecule in a biological process in vitro is to compare the cellular process in the absence and the presence of the molecule by inhibiting its expression. Furthermore, inhibiting expression of a target molecule in vitro is routinely performed using antisense oligoncucleotides. It would have been obvious to one of ordinary skill in the art to inhibit the expression of SEQ ID NO: 33 using antisense oligonucleotides in vitro because the nucleotide sequence of human neurilin had been taught previously by He et al and the methods for inhibiting a target gene of known sequence using antisense had been taught previously by Milner et al. One of ordinary skill in the art would have expected that antisense between 15 and 50 nucleobases that are targeted to SEQ ID NO: 33 would inhibit neuropilin expression in vitro since the routine inhibition of target gene expression using antisense in vitro was shown previously my many in the field, including Milner and Baracchini (for target genes of known nucleotide sequence). It would have been obvious to one of ordinary skill in the art to incorporate the various nuclease resistant modifications into the antisense oligonucleotides, including phorphorothioate internucleotide modifications, morpholino backbone structures, alkyl or heterocyclic intersugar linkages, 2'-O-ribonucleotides and

modified bases such as hypoxanthine into the antisense oligonucleotides because Baracchini taught the incorporation of such modifications into oligonucleotides and one of ordinary skill in the art would expect such modifications to enhance antisense stability and target binding, as taught by Baracchini et al. Milner et al additionally have taught methods of designing and evaluating antisense which target different regions of a target gene of previously disclosed sequence for their ability to inhibit a target gene in vitro. One of ordinary skill in the art would have been motivated to inhibit the expression of human neuropilin of SEQ ID NO: 33 because neurilin plays a role in various cellular and developmental processes, including neurite outgrowth and organogenesis, as taught previously by He et al. Inhibiting the expression of neuropilin in cells in vitro using antisense would provide a means to compare the cellular process of neurite outgrowth (axonal repulsion) in the absence and presence of neuropilin, thereby providing insight into how the process of neurite outgrowth is affected by the participation of this target gene. It would have been obvious to administer a vector encoding antisense targeting human neuropilin to inhibit the target gene=s expression in an appropriate target cell in vitro because incorporation of a nucleotide sequence into an appropriate vector for expression in a target cell is routine in the art and one would expect that an appropriate vector would allow for expression of the antisense sequence within the target cell, leading to target gene inhibition in vitro. One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al and Baracchini et al, would successfully be used for the in vitro inhibition of neurilin

expression, because in vitro methods of screening a known target gene for antisense inhibition is routine in the art. The disclosure of He et al, combined with the teachings of Milner and Baracchini in disclosing the routine empirical screening of antisense for their ability to inhibit expression of any RNA target, render the instant invention obvious

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Applicant's arguments filed 4-7-05 have been fully considered but they are not persuasive. Applicants argue that the prior art does not suggest or motivate one to combine the teachings of He, Milner and Baracchini (and Soker). Applicants assert that nothing in the teachings of He to link the target gene encoding neuropilin with either VEGF or tumor formation. Applicant also argues that the instant invention as a whole is not rendered obvious by the teachings of He, Milner and Baracchini because of the inherent property of the subject matter claimed and disclosed in the specification, which inherent property is the ability of the antisense oligonucleotides to inhibit tumor growth by inhibiting the expression of neuropilin.

The claimed invention is drawn to compositions comprising antisense to neuropilin, but is not drawn to methods of inhibiting tumor growth. And so, contrary to Applicants' assertions, the combined references render the instant invention obvious for the following reasons: He teaches the nucleotide sequence of the target neuropilin gene and its role in neurite outgrowth and organogenesis, thereby teaching the motivation to study the involvement of neuropilin in these biological processes. Soker et al teach the correlation between angiogenic factors, including various VEGF isoforms,

and vascularization-dependent tumor growth (see pages 5761-5762). Soker et al teach the possible role of neuropilin in tumor vascularization and/or metastasis. Soker et al also teach the motivation to study the various affinity/molecular mass VEGF receptors, including neuropilin or $VEGF_{165}$, with respect to their potential biological roles in tumor vascularization and metastasis. Milner teaches the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). The teachings of He, combined with the routine use of antisense oligonucleotides for inhibiting target gene expression, render the instant invention obvious to one of ordinary skill in the art of molecular biology (see Milner at 537, who teaches a combinatorial technique that allows simultaneous assessment of all possible oligonucleotides within a given region to identify sequences open to duplex formation and antisense inhibition of target gene expression: "...the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence."

Regarding the inherent characteristics of a previously disclosed compound or compositions, or one that is rendered obvious by a combination of references previously disclosed, as in the instant case, Applicant is reminded of the reasoning relied upon in addressing inherent properties, albeit in the situation where Applicant seeks to distinguish a claimed invention from one previously taught in the prior art: See *In re* Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an

applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, absent evidence to the contrary, since the oligonucleotides rendered obvious by the teachings of He, Milner and Baracchini meet all of the structural limitations of the instantly claimed invention, it would necessarily be presumed to have the functionality claimed, of inhibiting tumor cell growth (*e.g.* in vitro).

In addition, the examples 4 and 5, col. 17-18, of Baracchini teach the use of cellular assays for the routine determination of antisense inhibitory activity, render the instant invention obvious. This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). There is no requirement to link the different and distinct target genes VEGF and neuropilin in order to provide a proper motivation for designing and assessing antisense to study the role of neuropilin in the biological processes in cells including organogenesis and neurite outgrowth. The routine screening techniques

taught by both Milner and Baracchini apply to utilizing antisense to inhibit any target gene of known nucleotide sequence. There is no particular need to link tumor growth to neuropilin (although a lack of proper regulation of organogenesis can result in tumor formation), since the obviousness rejection addresses antisense compositions, not methods of inhibiting tumor growth.

Applicants argue that the instant invention is not obvious because the prior art (He) does not teach the inhibition of expression of neuropilin, but instead teaches inhibition of neuropilin on a protein level. Applicants are correct that He does not teach the inhibition of expression of neuropilin, but, contrary to Applicants' assertions, inhibition of expression of a particular protein is a routine way of investigating that protein's biological role in cellular processes. And while many avenues exist to study a candidate molecule's biological role(s), including inhibition of expression and inhibition of activity on a protein level, inhibition of expression of a protein using antisense is routinely chosen as an experimental approach, as evidenced by the teachings of Milner and Baracchini.

Applicants argue that no reasonable expectation of success exists with regard to antisense and their ability to target and inhibit the expression of neuropilin. Contrary to Applicants' assertions, the combinatorial technique taught by Milner, and the previously disclosed nucleotide sequence of neuropilin (by He), allow for a simultaneous assessment of all possible oligonucleotides within a given region to inhibit target nucleic acid expression. The lack of correlation of predicted secondary mRNA structure with successful antisense inhibition was brought to light by the teachings of Milner, but this

lack of correlation does not make the routine screening method for finding effective inhibitory antisense any less routine, it simply warns that one cannot design antisense based simply on secondary structural predictions. The quantity of data existing in the scientific literature (*e.g.* see Baracchini) showing antisense inhibition to various target genes well illustrates that a reasonable expectation of success exists in finding antisense to target and inhibit a target gene of known sequence.

Allowable Subject Matter

SEQ ID NOS: 1-3, 5, 6, 8-12 are free of the prior art searched and of record. Claims 6-9, 17-19, 23-25, 30, 32, 42-44, 45, 47-51, 57, 59, 61 appear free of the prior art searched and of record.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ∋ 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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